FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
FDA White Oak Campus, Building 31, The Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland
March 28 – 29, 2012

QUESTIONS TO THE COMMITTEE

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1. (DISCUSSION) The current draft obesity drug guidance document recommends that at least 3000 patients be randomized to investigational drug therapy and at least 1500 to placebo in one-year phase 3 trials. To date, most of the patients enrolled in the phase 2 and 3 clinical trials for investigational obesity drugs have very low short-term risk for major adverse cardiovascular events (MACE) (e.g., < 0.5% per year).

   Discuss the potential strengths and weaknesses of enriching the phase 2 and 3 clinical trials with overweight and obese individuals at higher risk for CV events (e.g., history of myocardial infarction, stroke, multiple risk factors) and performing a meta-analysis of prospectively adjudicated MACE.

2. (DISCUSSION) For drugs with a signal for potential CV harm, it should be assumed that sponsors will be required to rule out a certain degree of excess CV risk; e.g., through conduct of a dedicated CV outcomes trial (CVOT) prior to market approval.

   Discuss the potential strengths and weaknesses of the following design parameters of a CVOT for an obesity drug:

   a. Ruling out a certain degree of excess CV risk with a pre-approval analysis of a fraction of the planned number of total events, followed by ruling out a smaller excess CV risk with the post-approval final analysis. This assumes that the pre-approval analysis will be based largely on data obtained during the first year of patient exposure, a period of fewer drop outs and maximal weight loss.

   b. Setting non-inferiority margins for excess CV risk on the basis of risk difference versus relative risk.

   c. Primary endpoint of strict MACE (CV death, nonfatal MI, nonfatal stroke) versus MACE-Plus (e.g., hospitalized unstable angina, emergent coronary revascularization).

   d. Primary analysis population that incorporates on-treatment and off-treatment information (total time analysis population) versus a population that incorporates only on-drug information (on-drug analysis population).

   e. Discontinuing from study drug patients who do not achieve a certain degree of weight loss within the first 3 to 6 months of the trial. Those withdrawn from study drug would continue to be followed.

QUESTIONS TO THE COMMITTEE (cont.)

3. (VOTE) Do you believe that obesity drugs without a theoretic risk or signal for CV harm should be required to rule out a certain degree of excess CV risk with a CVOT or an appropriately sized meta-analysis of phase 2 and 3 MACE data?

   a. If you voted "No", please explain why

   b. If you voted "Yes", please discuss how (CVOT or meta-analysis or both) and when such data should be obtained:

      i. Pre-approval
      ii. Pre- and post-approval (two-staged approach with different non-inferiority margins pre- and post-approval)
      iii. Post-approval